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Effectiveness of different diagnostic tools for upper urinary tract urothelial carcinoma

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ABSTRACT

Objective: The results of urinalysis, radiographic studies, urinary cytology examinations, and ureterorenoscopy (URS) biopsies, as well as the results of histopathology can be used to establish a diagnosis of upper urinary tract urothelial carcinoma (UTUC).

Materials and Methods: We enrolled 99 patients who underwent radical nephroureterectomy (RNU) during the period 2003–2007. A total of 65 random urine and 83 URS washing cytology examinations, 48 intravenous urography (IVU), 59 retrograde pyelography (RP), and 81 URS biopsy results were available prior to RNU and were compared with the pathological grades and stages of these surgical specimens.

Results: Ninety-three UTUCs were found among the 99 RNU specimens. Initial presentations and urinalysis results could not predict tumor stages. The patient with preoperative pyuria was significantly associated with high-grade UTUC (75.0% vs 52.6%, $p = 0.031$). Random urine and URS washing cytology results could not predict tumor grades or stages. The sensitivity of 3-day random urine cytology was significantly better than 2-day and 1-day examinations ($p = 0.002$ and $p = 0.019$, respectively). The abnormal findings in IVU and RP accounted for 89.4% and 100%, respectively. Non-enhancement of images was significantly associated with high tumor grading ($p = 0.01$). URS biopsy ($n = 72$) was positive for malignancy in 52 patients (69.3%). Biopsy grade had a significant correlation with surgical tumor grade ($\kappa = 0.649$) and high-grade biopsy results were significantly associated with invasive tumor stage (pT2–T4) ($p = 0.004$).

Conclusion: Combining random urine cytology for 3 nonconsecutive days, upper urinary tract images, and URS biopsies provided an accurate diagnosis of UTUC. This study found that preoperative pyuria in urinalysis, non-enhancement in IVP or RP, and high-grade tumor in URS biopsy could predict high-grade tumor in RNU specimens.

1. Introduction

The incidence of upper urinary tract urothelial carcinoma (UTUC) is high in Taiwan.[1] Worldwide, UTUC, including carcinomas of the renal pelvis and ureter, only accounts for 4–5% of all urothelial cancer.[2,3] However, in Taiwan, the ratio of renal pelvic urothelial carcinoma (UC) to ureteral UC, and to bladder UC is 1.2:1:6.7, which means UTUC is close to 25%.[4] Previous studies showed that 31.2–34.1% of UTUC patients developed metachronous bladder UC after radical nephroureterectomy (RNU) and bladder cuff resection, the gold standard for treatment of UTUC.[5,6]

A diagnosis of upper urinary tract tumor is based on results of urinalysis, urine cytology examination, upper urinary tract imaging, endoscopic inspection, and biopsy for histopathological analysis.[7,8]

We retrospectively reviewed patients receiving RNU and bladder cuff resection because of suspected upper urinary tract tumor after the ureterorenoscopy (URS) examinations, and investigated the sensitivities of urinalysis, random urine cytology, upper urinary tract washing cytology, intravenous urography (IVU), retrograde pyelography (RP), URS inspection, and biopsy in the detection of UTUC in Taiwan. We also correlated these diagnostic tools with the pathological staging and grading of UTUC to determine the effectiveness of these examinations.

2. Methods

From 2003 to 2007, 99 patients received RNU and bladder cuff resection after URS examination in our institution. None of the patients had a history of bladder or upper urinary tract UC. All of

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the patients submitted a urine specimen for dipstick and microscopic analysis prior to URS.

Microscopic hematuria was defined as red blood cell counts >5 under high-power field and pyuria was defined as white blood cell >5 under high-power field. Proteinuria was defined as urine concentration of protein of ≥30 mg/dL.

Other surveillance techniques included random urine cytology, IVU, RP, computed tomography (CT), magnetic resonance image (MRI), URS washing cytology, and URS biopsy. Positive findings of random urine cytology and washing cytology included at least one specimen with suspicious malignant cells or atypical cells. The abnormal findings of the image studies included obstructive uropathy, urinary tract filling defect, and visible tumors in the radiographic examinations.

The combination of these surveillance tools depended on the patients' conditions and the physicians' choices. Of the 99 patients, 99 urinalysis results, 65 random urine cytology results, 48 IVU results, 59 RP results, 81 CT results, 17 MRI results, 99 URS examinations, 83 URS washing cytology results, and 81 biopsy results were available.

The χ^2 test was used to analyze associations between diagnostic tools and pathological parameters. The interobserver agreement between URS and RUN pathological results was evaluated using the Cohen's κ method. A p value <0.05 was considered statistically significant.

3. Results

Of the 99 patients who received RNU and bladder cuff resection due to diagnosis or suspicion of UTUCs, six had RNU specimens without UC. Two of the patients had URS biopsy specimens that revealed superficial low-grade UC without lamina propria invasion. Two of the patients had renal cell carcinomas. The other two patients had biopsy specimens that showed mesenchymal polyps and papilloma, respectively.

Ninety-three patients had pathologically proven UC in the upper urinary tract, including 49 women (52.7%) and 44 men (47.3%). The median age of all UTUC patients was 69 years (interquartile range, 58–74 years). UC was found on the left side in 47 patients (50.5%), on the right side in 44 patients (47.3%), and on both sides in two patients (2.2%). UC was located only at the renal pelvis in 40 patients (43.0%), only at the ureter in 31 patients (33.3%), and at both renal pelvis and ureter in 22 patients (23.7%).

A total of 93 urinalysis results, 62 random urine cytology results, 47 IVU results, 54 RP results, 78 CT results, 16 MRI results, 93 URS examinations, 77 URS washing cytology results, and 75 biopsy results were available in the cohort of 93 UTUC patients.

3.1. Initial presentations and urinalysis

Initial presentations are listed in Table 1. The most common symptom was gross hematuria in 71 patients (76.3%). Eleven patients (11.5%) visited urology clinics because abnormal findings had been disclosed at hospitals elsewhere, including microscopic hematuria, renal function impairment, anemia or hydronephrosis, and ultrasonographic evidence of a renal mass.

Urinalysis was obtained prior to URS studies and showed microscopic hematuria in 67.7% (n = 63), pyuria in 38.7% (n = 36), and proteinuria in 34.4% (n = 32) of patients (Table 1). Initial presentations and urinalysis results could not predict tumor staging. Interestingly, patients with pyuria had a significantly higher percentage of high-grade UC (75.0% vs 52.6%, p = 0.031).

Table 1
Initial presentations and urinalysis in upper urinary tract urothelial carcinoma patients.

	Results	n (%)
Initial presentation (n = 93)	Gross hematuria	71 (76.3)
	Flank pain or soreness	22 (23.7)
	Abdominal discomfort	5 (5.3)
	Abnormal findings in health examination[a]	11 (11.5)
	Body weight loss	3 (3.2)
	Recurrent UTI	2 (2.2)
Urinalysis (n = 93)	Microscopic hematuria	63 (67.7)
	Pyuria	36 (38.7)
	Proteinuria	32 (34.4)

UTI = urinary tract infection.
[a] Abnormal findings in health examination included microscopic hematuria, hydronephrosis, renal mass, elevated creatinine, and anemia.

3.2. Cytology

Random urine cytology and URS washing cytology results were available for 62 patients and 77 patients, respectively. The sensitivity of random urine cytology and URS washing cytology was 58.1% and 58.4%, respectively (Table 2). Thirty-nine patients submitted random 3-day urine cytology specimens, nine patients submitted 2-day results, and 14 patients submitted 1-day results. The sensitivity of 3-, 2-, and 1-day collection of random urine cytology results was 74.4%, 33.3%, and 28.6%, respectively. Three-day random urine cytology was significantly better than 2- and 1-day urine cytology (p = 0.002 and p = 0.019, respectively); however, there was no difference between 2- and 1-day urine cytology sensitivity (p = 0.809).

The contributions of high pathological grade and invasive tumor stage stratified by results of random urine cytology and upper urinary tract washing urine cytology are listed in Table 2. There were no associations between cytology collecting methods or predictions of tumor grading and staging.

3.3. Upper urinary tract imaging

Of the 47 patients with IVU prior to URS examinations, 19.1% had hydronephrosis, 19.1% had non-enhancement of upper urinary tract, 51.1% had urinary tract filling defects, and 10.6% had no definite abnormal findings. A total of 54 patients received RP following URS studies. The procedures showed hydronephrosis in 7.4%, non-enhancement of upper urinary tract in 3.7%, urinary tract filling defects in 88.9%, and no definite abnormal finding in any of the patients.

The contributions of pathological results in IVU and RP characteristics are demonstrated in Table 3. Non-enhancement in the upper urinary tract group had significant superiority over the no definite abnormal finding group in predicting high tumor grading (p = 0.01). The results of CT were available in 78 patients and showed simply hydronephrosis, suspected upper urinary tract tumors, and no definite abnormal findings in seven (9.0%) patients, 70

Table 2
Urine cytological and pathological results.

	Cytology results, n (%)		High-grade UC (%)		Invasive tumor (%)	
Random urine cytology (n = 62)	Negative	26 (41.9)	50.0	p = 0.121	42.3	p = 0.96
	Positive	36 (58.1)	69.4		41.7	
URS washing cytology (n = 77)	Negative	32 (41.6)	46.9	p = 0.053	34.4	p = 0.1
	Positive	45 (58.4)	68.9		53.3	

UC = urothelial carcinoma; URS = ureterorenoscopy.

Table 3
Upper urinary tract images and pathological results.

	Characteristics	*n* (%)	High-grade UC (%)	Invasive tumor[a] (%)
IVU ($n = 47$)	No definite abnormal finding	5 (10.6)	20.0	20.0
	Hydronephrosis	9 (19.1)	55.6	44.4
	Non-enhancement	9 (19.1)	88.9	66.7
	Filling defects	24 (51.1)	58.3	41.7
RP ($n = 54$)	No definite abnormal finding	0 (0)	0	0
	Hydronephrosis	4 (7.4)	50	50
	Non-enhancement	2 (3.7)	100	50
	Filling defects	48 (88.9)	60.4	47.9

IVU = intravenous urography; RP = retrograde pyelography; UC = urothelial carcinoma.
[a] Invasive tumor was defined as pathological tumor stage T2–T4.

(89.7%) patients, and one (1.3%) patient, respectively. Sixteen patients underwent MRI and all of them showed suspected upper urinary tract tumors. The upper urinary tract imaging provided limited information in predicting tumor grading and the depth of tumor invasion.

3.4. URS inspection and biopsy

URS inspection of suspected upper urinary tract tumor was documented in 82 (88.2%) patients and URS biopsies were performed in 75 (81.6%) patients. The histopathological results of URS biopsies are listed in Table 4. Fifty-two biopsy specimens were found to be UCs, including 24 (46.2%) of low grade and 28 (53.8%) of high grade. The UC detection rate of URS biopsy was 69.3%. Of the 52 patients with UC in URS biopsy specimens, there was a significant correlation between URS biopsy grade and final tumor grade ($\kappa = 0.649$, $p < 0.001$).

After examination of the RNU specimens, pathological stage Tcis, Ta, T1, T2, and T3 accounted for 2.2% ($n = 2$), 25.8% ($n = 24$), 25.8% ($n = 24$), 14% ($n = 13$), and 32.2% ($n = 30$), respectively (Table 5). Of the patients with low- and high-grade UC in URS biopsy, the percentages of invasive UC were 20.8% and 60.7%, respectively. The high-grade tumor in URS biopsy was significantly associated with invasive tumor stage in RNU specimens ($p = 0.004$). Lamina propria was noted histologically in only three URS biopsy specimens, including two Ta stage and at least one T1 stage lesions. Seventy-two (96%) URS biopsy specimens showed only superficial layers in urothelial tumors and seemed to be not available to evaluate the accurate depth of malignant invasion.

4. Discussion

The standard treatment for UTUC is RNU with bladder cuff resection. Recently, some studies proposed the idea that conservative treatment with endoscopic laser ablation is safe and effective

Table 4
Histopathological results of ureterorenoscopy biopsies.

Results	*n* (%)
Low-grade UC	24 (32.0)
High-grade UC	28 (37.3)
Papillary urothelial neoplasm with low malignant potential	5 (6.7)
Chronic inflammation	5 (6.7)
Atypical urothelial cells	4 (5.3)
Dysplasia	3 (4.0)
Inadequate specimens for diagnosis	3 (4.0)
Hyalinization	1 (1.3)
Reactive changes	1 (1.3)
Muscular hypertrophy	1 (1.3)

UC = urothelial carcinoma.

Table 5
Correlation between pathologic results of URS biopsies and RNU specimens.

			URS biopsy, $n = 52$		
			Low-grade UC $n = 24$ (46.2%)	High-grade UC $n = 28$ (53.8%)	
RNU specimen	Tumor grade, *n* (%)	Low	18 (75.0)	3 (10.7)	$p < 0.001$
		High	6 (25.0)	25 (89.3)	
	Tumor stage, *n* (%)	Tcis, Ta, T1	19 (79.2)	11 (39.3)	$p = 0.004$
		T2–T4	5 (20.8)	17 (60.7)	

RNU = radical nephroureterectomy; UC = urothelial carcinoma; URS = ureterorenoscopy.

in selected cases with low-grade, low-stage disease.[9] Thus, accurate preoperative grading and staging with the available diagnostic information is of great importance. Li et al[6] reported that tumor stage was a significant predictor of cancer-specific survival in Taiwanese UTUC patients.

The detection of UTUC cannot be achieved by a single diagnostic tool. At initial assessment, patients often present with microscopic hematuria. Standard assessment includes cystoscopy, upper urinary tract imaging, and urine cytology, followed by RP, endoscopy, and biopsy.[10] The regimen with cystoscopy, urine cytology, upper tract imaging, and RP can establish the diagnosis in 50–60% of patients. The accuracy increases to 80–90% with URS.[11] In our study, the sensitivity of urine cytology, washing cytology, IVU, RP, CT, MRI, URS inspection, and URS biopsy was 58.1%, 58.4%, 89.4%, 100%, 98.7%, 100%, 88.2%, and 69.3%, respectively. Urine cytology, IVU, and RP achieved the diagnosis of suspicious UTUC in 96.7% of patients. These diagnostic tools compensate for the weakness of other methods.

In our study, initial presenting symptoms, microscopic hematuria, and proteinuria had no correlation with tumor staging and grading. Recently, studies have noted that patients with chronic kidney disease had a worse prognosis and higher proportion of high-grade tumor with UTUC than those with normal renal function.[4] As for proteinuria, an indicator of chronic kidney disease, we did not notice any significant correlation between proteinuria and tumor grade/stage. However, patients with pyuria had a significantly higher percentage of high-grade tumor than those without pyuria.

The European Association of Urology guidelines on the diagnosis of UTUC suggest that IVU is the first choice for investigating hematuria, that RP might be useful in cases with equivocal IVU findings, and that CT might be difficult to diagnose accurately small-volume tumors in the renal pelvis or ureter.[12] Cowan et al[13] documented that the sensitivity of CT and RP in the diagnosis of UTUC was 97% and 93%, respectively, and CT should be used before RP as a noninvasive comprehensive tool. The sensitivity of these upper urinary tract images was similar in our study. Previous studies have shown that poor visualization of the renal collecting system in IVU is an indicator of invasive UTUC.[14] We noted that the non-enhancement presentation in IVU had a special predictive value for a high-grade tumor. Although the upper urinary tract imaging was not effective in predicting tumor grading and the depth of tumor invasion in our results, CT/MRI scans still play an important and essential role for cancer staging to detect tumor invasion to adjacent organs/tissue, lymphadenopathy, or distal metastases.

Previous studies have stated that the sensitivity of urine cytology is poor in low-grade tumors and better in high-grade tumors.[15] We noted that the sensitivity of random urine cytology in high- and low-grade tumors was 65.8% and 45.8%, respectively, although without any significant difference. After identifying the patients with three sets of cytology results, the sensitivity in high- and low-grade tumors was elevated to 76% and 71.4%, respectively, still without a significant difference. Skolarikos et al[16] stated that

the combination of exfoliated cell cytology and URS biopsy improved the predictive power of the final pathological grade and stage. Although we noted that the percentage of high-grade tumor was higher in patients with positive random urine cytology or positive washing cytology, and the percentage of invasive tumor was higher in those with positive washing cytology, these findings did not reach significance, possibly due to the limited case numbers. However, as for random voided urine cytology, three sets of specimens yielded significantly higher sensitivity than one or two sets of specimens. The noninvasive collection of three sets of random urine cytology in three nonconsecutive days had a sensitivity of 74.4%, which was even better than ureteral/renal pelvic washing cytology.

Huben et al[2] noticed tumor grade (low/high) matched tumor stage (superficial/invasive) in 83% of UTUC, and both tumor stage and grade were predictive of prognosis. We found that tumor grade (low/high) matched tumor stage (Ta, Tcis, T1/T2–4) in 69.8% with statistical significance, and URS biopsy grade also matched stage in 69.2% with statistical significance. However, the sensitivity of URS biopsy, 69.3%, was not satisfactory. Guarnizo proposed that a multi-biopsy approach could improve diagnostic accuracy. With each lesion biopsied 2–6 times, the tissue diagnosis of UC was achieved in 89%, and the biopsy results matched the exact tumor grade in 78%.[17]

In conclusion, accurate diagnosis of UTUC should combine urine cytology, upper urinary tract images, URS inspection, and biopsy. Collecting random voided urine for three nonconsecutive days could significantly elevate the sensitivity. Pyuria in urinalysis, nonenhancement in IVU or RP images, and high-grade URS biopsy could predict high-grade tumor.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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